

**Remarks**

Entry of the foregoing and reconsideration of the application identified in caption as amended, pursuant to and consistent with the Rules of Practice in Patent Cases, and in light of the remarks which follow, is respectfully requested.

By the present amendment, claims 1-4, 6, 8, 10, and 12 have been amended, so that claims 1-12 will remain pending upon entry of the present amendment.

The Examiner has objected to the range of 0.25-0.5 mg as set forth in claims 6 and 10 as not finding support in the specification. The subject matter present in the claims as originally filed provides support for those claims. Thus, the specification has been amended to insert the compositional ranges as originally filed, which includes the range recited in present claim 6.

The claims and specification have been objected to regarding the misspelling of the compound known as vitamin B5. These typographical errors have been corrected by changing “Calcium d-Panthotenate” to “Calcium d-Pantothenate” where appearing throughout the specification and claims.

Accordingly, no new matter has been presented by the present amendments. Withdrawal of the record objections is respectfully requested.

Claims 1 and 2 stand rejected under 35 U.S.C. § 112 and § 101 as being improper process claims for not setting forth any steps. This rejection is respectfully traversed.

Claims 1 and 2 have been amended to recite the step of “administering a composition” to “substantially healthy human skin” and thus, recite proper method steps in a manner set forth to comply 35 U.S.C. § 112 and § 101. The expression “*to maintain health and beauty*” in claim 1 has a support at least on page 2, line 6 and then line 9 of the specification. Withdrawal of the record rejections of claims 1 and 2 under 35 U.S.C. § 112 and § 101 is respectfully requested.

Claims 8 and 12 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for including the phrase “such as.” This rejection is respectfully traversed.

The rejection of claims 8 and 12 under 35 U.S.C. § 112 has been overcome by amending these claims to replace the phrase “such as” with the word “of.” Withdrawal of the record rejection of claims 8 and 12 under 35 U.S.C. § 112 is respectfully requested.

Claims 3, 4, 7, 8, 11 and 12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by either of Raisfeld (US 4,507,321); Charonis et al. (WO 94/12464); Ilenchuk et al. (WO 99/51213); or Minoshima et al. (JP 07/268,323). Claims 3, 4, 8 and 12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by either of Eckart et al. (EP 0,884,046); Wolf et al. (WO 98/06376); Hahn et al. (WO 96/23490); or Matsubara et al. (JP 2003/113047). These rejections are respectfully traversed.

The Examiner has cited the various prior art references for the disclosure of dietary, pharmaceutical, or cosmetic uses of spermine and/or spermidine in humans. Claims 1-12 have been amended to more particularly point out that substantially healthy human skin is treated with spermine and/or spermidine in free or salified form as active principle to improve hydration of the human skin to maintain health and beauty thereof.

Applicants submit a sworn statement in the form of an Affidavit signed by an expert, co-inventor, Dr. Fabio Rinaldi. Dr. Rinaldi observes that the capacity of the skin to keep an adequate hydration state, that is to withhold water at the stratum corneum of the epidermis, is a fundamental property to maintain healthy conditions, and is independent from cell regeneration processes and ageing.

The clinical study described therein provides evidence that the new use as proposed is to maintain health and beauty of the skin. This means that skin in normal, unaffected (non pathological) conditions is concerned.

Under "Assessment of hydration", the effectiveness of a composition of the invention comprising spermidine was assessed *in vivo* on the skin of 20 adult consenting volunteers aged between 18 and 55. This shows that the subjects treated in the study are healthy volunteers and include young subjects. This is also confirmed by the enclosed abstract from the clinical study where the inclusion criteria in the study are presented in the last paragraph thereof. Therefore, neither pathological conditions of the skin, nor treatment of aged skin are concerned in this study.

Having said that, it should be noted that in such study skin hydration was measured by means of a corneometer. The corneometer is an instrument for measuring stratum corneum moisture, that is the hydration of the outermost layer of the skin. It measures the electrical capacitance of the skin surface as an indicator of stratum corneum hydration. The corneometer results in the study showed an increase in skin hydration with a statistically significant difference between the mean values observed after treatment and the

corresponding values observed after the placebo. The degree of hydration, determined by electric capacitance measured with the corneometer, increased by over 10% with a high statistical significance ( $p < 0.001$ ).

As a result from all the above considerations, it follows that the invention according to the amended claims specifically refers to the improvement of hydration in the outermost layer of human skin not suffering from pathological conditions and not necessarily an aged skin.

Claims 1-12 thus concern novel and inventive subject matter with respect to the prior art, which art all refers to treatment of skin in pathological conditions, or aged skin. Indeed the prior art cited under § 102 relates to cell regeneration processes in pathological or damaged skin. None of the prior art documents describe or suggest that spermine and/or spermidine in free or salified form can be active as cosmetics inasmuch as they withhold water at the stratum corneum of the epidermis, so that they can improve hydration of the human skin to maintain health and beauty in normal subjects, even in young normal subjects.

The expert's conclusion is: "*I do not believe that the effect of spermidine in determining and keeping an adequate hydration of the skin under physiological conditions, i. e. independently from the presence of a skin pathology in which the keratinocytes and the skin fibroblasts need to be modulated (by means of up or down-regulation), may at all be predictable from the prior art*".

Prior art which relates to nail strengthening or hair conditioning are even less relevant.

The enclosed sworn statement of Dr. Rinaldi shows that the above-noted property as studied and claimed in the present application is not implicit to a person skilled in the art in what is expressly mentioned in the cited documents, which concern cell regeneration processes in pathological or damaged skin.

As to Eckart in particular, this reference relates to a photo protective composition wherein the active principles are vitamins A and C, and a natural polyamine is only found to be a useful co-agent. Although this is the only cited prior art mentioning skin moisture, Eckart does not disclose the cosmetic use of spermine and/or spermidine in free or salified form as the active principle to improve hydration of the human skin to maintain health and beauty thereof.

Indeed, Eckart belongs to the category of prior art where the skin is affected by a pathological agent, in this case UV irradiation. In this regard, the enclosed abstract from the clinical study entitled "Assessment of hydration" of the present application shows the criteria for including those volunteers in the study. In fact:

- The active principle spermidine (trihydrochloride) in the study is also referred to as Biogenine.
- Under 3.b., Inclusion criteria, it is required that they should be healthy.
- Under 3.e., Restrictions, it is required that they should not be exposed to UV rays.

This confirms that the technical problem at issue in the present application is not to combat the effect of UV irradiation on the skin, rather it is to treat substantially healthy skin..

On the other hand, Example 1 of Eckart is directed to the situation where irradiation of the skin with UV is required to experimentally test the activity of the photo protective composition of D4 including vitamins C and E as active principles, and spermine is added as an enhancer at a lower concentration (on the order of ppm). In the end, Eckart shows how to enhance the photo protective activity of the active principles vitamins C and E on skin irradiated with UV.

The hydration improvement on healthy, non irradiated skin, resulting from the clinical study in the present application has therefore a different effect, as generally explained in Dr. Rinaldi's Affidavit.

Withdrawal of the record rejections of Claims 3, 4, 7, 8, 11 and 12 under 35 U.S.C. § 102(b) is respectfully requested.

Claims 5, 6, 9, and 10 stand rejected under 35 U.S.C. § 103 as being obvious over Minoshima et al. (JP 07/268323) in view of Henderson (WO 00/37087) and Ioannides (WO 02/15860). This rejection is respectfully traversed.

Regarding non obviousness, the enclosed sworn statement of Dr. Rinaldi shows on the one hand that the above property as studied and claimed in the application in question, i.e. the capability of spermine and/or spermidine of withholding water at the stratum corneum of the epidermis in non pathological or non-aged conditions, is not implicit to a person skilled in the art in what is expressly mentioned in the cited documents which concern cell regeneration processes in pathological or damaged skin.

It also shows on the other hand that such property studied and discussed under the clinical study "Assessment of hydration" in the description, i.e. the capability of spermine and/or spermidine of withholding water at the stratum corneum of the epidermis in non pathological or non-aged conditions, is not predictable or evident to a person skilled in the art from the cited documents which concern cell regeneration processes in pathological or damaged or affected skin.

It should be furthermore considered that — inasmuch as this property of withholding water at the stratum corneum of the epidermis in non pathological or non-aged conditions is concerned -spermine and spermidine are a selection made by the Applicants from a wide rage of polyamines. There is no indication in the prior art about any selection in the polyamines to provide a special property which is not simply and broadly cell renewal in pathological or damaged skin.

Accordingly, it would not have been obvious to pick and choose components from the disclosure of three different references to arrive at the claimed invention.

Withdrawal of the record rejection of Claims 5, 6, 9, and 10 under 35 U.S.C. § 103 as being obvious over Minoshima et al. (JP 07/268323) in view of Henderson (WO 00/37087) and Ioannides (WO 02/15860) is respectfully requested.

From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is hereby earnestly solicited.

Respectfully submitted,

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